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Title of Invention	The persistence composition containing somatotropin.

Abstract

The present invention is to provide the composition possibling the transplant administration which is manufactured after the pododerm process after granulating the in vivo activity somatotropin by using the water-soluble polymer of 1 kinds emitting somatotropin in vivo to the persistence.

Representative Drawing(s)

Fig. 1

Description

[Title of invention]

The persistence composition containing somatotropin.

[The simple description of the drawing]

The first drawing the graph according to the table 1. Figure 2 is a graph according to the working example 1 of the table 1 and table 2. Figure 3 is a graph according to the table 3.

[The detailed explanation of invention]

The invention relates to the persistence composition containing somatotropin. And particularly, it is about the composition which continuously releases the somatotropin having in vivo activity it dosed someboby with to mammal to parenteral. It stimulates liver and the foreign material is created the somatomedin - 1 (somatomedin-1) to a kind of the polypeptide consisting of the amino acid of 191 having somatotropin is the activity in vivo. With again raising the growth of the bone and muscle and promoting the growth of animal this compound is known as. In the most of the somatotropin having in vivo activity is in vivo, the half life shorts. Therefore in order to make maintain the during the period the effect in which the biological phosphorus effect is shown enough and wanting at the same time, the excess of quantity has to be medicated than the effective amount or since to enhancing the administration frequency, the big damage can be clothed upon the medication object. Therefore, by the composition which continuously released the material having in vivo activity according to this demand effect need to be ***ed for the long term to one administration in case of biologically dosing someboby with the active phosphate material to vivo being developed and minimizing the administration frequency the damage of the medication object was reduced. The research for canceling to troublesome according to the frequent administration had been being multilaterally included.

Up to date, after by the example mainly using the plant oil or the mineral oil as the scan format composition (injectable formula) in KR89-2631 B1 and KR87-1825 A, adding excipient and moisturizer and forming the thickened oil vehicle, it mixed the somatotropin of the transition metal complex and compositions which continuously released the in vivo activity material, especially, somatotropin tried to extend prolonged-release.

And in the dissimilar European patent application first 93, 917 and European patent application the 314, and 421, the example adding the in the water or the oil the carbohydrate polymer text in composition has. And in the dissimilar European Patent the 211, and 691, the plant oil and wax were added in somatotropin and the activity persistence at in vivo of somatotropin tried to be extended. And the composition in which the tocopherol acetate is mixed in and, KR90-1689 A and KR90-23104 A with the Homa taut lophine and which tries to extend the activity persistence at in vivo has. Biologically, disclosed is the method of the formulation about the transplant dosage composition (implantable formula) which icv is the active phosphate somatotropin the other method manufactures the barrier pododerm (Barrier Coating) which partly covers by using the shellac, the beeswax, and the material like the cellulose (Cellalose) in order to for example control the emission of somatotropin at KR90-6886 B1.

In KR86-65717 A dissimilar, since by using the sucrose and ethyl cellulose in the urine taut popin, the pellet (pelllet) being made and forming pododerm by here using the micropore polyethylene and comparison siege polyethylene, the persistence of somatotropin tried to be extended.

In WO WO90-11070 A another, by using the non-aqueous and insoluble polymer, pellet was manufactured and the persistence tried to be extended also. In the transplant dosage compositions for the above inventions, problems has in vivo in administration with the miss matching of the biological tissue in the organism retention since the cyst (encapsulation) phenomenon of composition by the fiber texture (fibrous tissue) is so therefore created the long longevity of residue.

Thus, because of had been study the transplant dosage composition (implantable formula) which as to these inventor,s icv biologically removed in vivo retention problem among method, the invention was completed.

That is, the invention relates to the granulation, here, the hydroxypropyl cellulose (hydroxy propyl cellulose) or the hydroxypropylmethylcellulose (hydroxy propyl methyl cellulose) the somatotropin (the manufacturing method is hereinafter described in the liposome somatotropin : KR23104 A) mixed with the water-soluble polymeric chain polyethylene glycol and somatotropin or (L) - alpha (α) - phosphatidylcholine is mixed. And granule was the pododerm (coating) and it manufactured with the refinement (tablet) or the pellet and the persistence was extended.

Hereinafter, the present invention is illustrated in detail as follows:.

After mixing material more than one kind or 2 kind and somatotropin or the selected liposome urine taut popin among the thing in which the molecular weight is 20,000 or greater among the polyethylene glycol, it here adds the water of little and it mixes and the invention the granulation. After using the spray thing (spray gun), the hydroxypropyl cellulose warmed up in the ethanol was injected in the granulated hybrid and hybrid was made evenly the pododerm (coating), the hybrid which became pododerm was put into the refining manufacture device system (tablet machine) and refinement or pellet was manufactured and the transplant dosage composition extending the persistence was completed.

Hereinafter, it thes same like next if the invention is explained more specifically based on the working example.

[Working example 1]

The somatotropin (hereinafter, the liposome right somatotropin) of the minor mixed in KR90-23104 A with - alpha - phosphatidylcholine manufactured was manufactured and it freeze-dried. While here hering the distilled water 5㎖ the propriety (titration) after mixing the molecular weight of polyethylene glycol (35,000) 10g and liposome right somatotropin 2.66g, it added and it remixed and granule was formed.

After the hydroxypropyl cellulose 10g being put and warming up in the ethanol 100㎖ with the homomixer (Homo-mixer), while ***ing the granule of the polyethylene glycol 35,000 and liposome right somatotropin, this solution 10㎖ is injected to the spray thing (spray gun). Without the pododerm solution granule is ***ed continuously after the jet finishes air was injected through the spray gun and the granule which became pododerm was desiccated.

By the fixed quantity and using the refining manufacture device system (tablet machine:KORSCH), built the diameter 0.9cm, and the refinement (tablet) of the thickness 0.2cm were manufactured.

The drug release test was done through the dissolution test manufactured. The used dissolution test instrument used the Caleva model number 7 ST (CALEVA Model 7ST). Condition was an order given with the solution container of the solution instrument of the dissolution test instrument with 10mM phosphate buffer (phosphate buffer solution) 400㎖, which the pH 7.3 very controlled by the NaOH the temperature 37℃, and the rotor (Roter) velocity surface 100rpm. Drug-releasing was measured in the wavelength (wave length) 280nm by using the spectrophotometer. The tyrosine, having in somatotropin phenylalanine, and tryptophan residues absorb the ultraviolet ray of 280nm and respective 275nm. Since the level combining these amino acids in somatotropin nearly constants, the concentration of somatotropin compares with to the absorbance at 280nm. In case of the pure somatotropin, when the route that the concentration of somatotropin is with 1mg / ㎖ and the ultraviolet ray passes through is 1cm, the absorbance at 280nm 1.0. Therefore, the concentration of somatotropin easily can calculate the quantity of emission since measuring the absorbance at 280nm. The equation in which somatotropin calculates the quantity of emission thes same like the lower part.

The capacity of the solution which the optical extinction measured at in the quantity of emission (mg) =280nm is used for the x dissolution test (㎖)

The capacity of solution (㎖)

Result showed for the table 1.

[Working example 2]

It manufactured with the method like the working example 1. And 5g was used instead of in *** 10g. And drug-releasing was measured at the method like the working example 1. Result showed for the table 1.

[Working example 3]

It did not become to the working example 1 in *** into the profile cellulose pododerm. And it mixed only the liposome right somatotropin and polyethylene glycol 35,000 two materials and refinement was manufactured like the working example 1. And drug-releasing was measured at the method like the working example 1.

Result showed for the table 1.

[Working example 4]

It manufactured with the method like the working example 3. But 7.565g was used instead of 10g. The chitosan 1.775g passing through the pulverizing device (pulverizer, Model AP-S) in which the powder size was pulverized to 0.7mm was added. And drug-releasing was measured at the method like the working example 1. Result showed for the table 1.

[Working example 5]

It manufactured with the method like the working example 3. But by using the right somatotropin instead of supplied separately the liposome right somatotropin, it mixed with the molecular weight 35,000 persons polyethylene glycol and refinement was manufactured with the refining manufacture device system. And drug-releasing was measured at the method like the working example 1. Result showed for the table 2.

[Working example 6]

It manufactured from the working example 5 with the method for thing same. But drug-releasing was measured at the method like the working example 1 while instead of using the molecular weight 20,000 persons polyethylene glycol the molecular weight 35,000 persons polyethylene glycol. Result showed for the table 2.

[Working example 7]

By instead of using the liposome porcine somatotropin in the working example 1 in the composition manufactured the liposome bovine somatotropin, the living body experiment (in vivo) was enforced. After using the method (Parapharyngeal method) performing an operation the limiting method of the female signal degrade rat roll hypophysectomy operation of about 80-100g pharynx surrounding as the animal used in experiment, it performed an operation, the weight was measured in the time to the same between 1 week like the daily and the rat without the change of the weight was assorted from by mouth 2 weeks. The skin which was cut after the refinement which manufactured like the working example 1 being equally divided as the same size 4 and the gastraeum subcutaneousness without the change of the weight of the rat 3 numbers being out cut a little and transplanting 1 (63.3mg) was sutured. The increased weight was shown when the same time weight everyday is compared with the weight of 3 days it measures and it transplants for the table 3. Ephemeris time, by using the rat 3 numbers without the change of the weight made into the method as in the above, nothing did not dose someboby with and it did an experiment on the control group.

시간(분)	실시예 1	실시예
15	0.1	0.4
30	2.1	8.0
45	3.6	12.0
60	4.8	17.2
75	6.0	20.0
90	8.0	23.6
105	9.6	26.0
120	12.0	29.6
150	13.6	3.16
180	15.2	33.6
240	17.6	11.0
300	21.2	
360	34.4	

시간(분)	실시예 5	
15	9.6	
30	17.6	
45	23.6	
60	28.8	
75	32.8	
90	37.2	
105	38.8	
120	40.0	
150		
180		

날짜(일)	투 석 수
1	6.83 ± 1.32
2	13.07 ± 0.64
3	15.67 ± 1.12
4	16.73 ± 1.01
5	18.80 ± 2.22
6	19.40 ± 1.47
7	18.77 ± 2.03

Scope of Claims

Claim 1 :

The prolonged release type composition of the somatotropin which is manufactured after the pododerm (coating) process it granulates the polyethylene glycol one kind or greater having the molecular weight 20,000 or greater the in vivo activity somatotropin is used can dose someboby with transplant.

Claim 2 :

The composition which is manufactured in order to include as to the first claim over the somatotropin 20 weight %.

Claim 3 :

The composition which characterizes to the urine taut popin extract from the hypothalamus of mammal and concentrate as to the first claim and be manufactured.

Claim 4 :

The composition which characterizes that somatotropin is manufactured as to the first claim with the DNA method for reassembly by microorganism.

Claim 5 :

Somatotropin as to the first claim, is the somatotropin of minor or the composition characterizing the porcine somatotropin.

Claim 6 :

The composition characterizing the animal growth hormone somatotropin is mixed as to the first claim with - alpha - phosphatidylcholine.

Claim 7 :

Composition wherein as to the first claim, the content of the polyethylene glycol is 80 weight% to 70 of the whole composition.

Claim 8 :

The composition in which the molecular weight of the polyethylene glycol characterizes 35,000 to 20,000 as to the first claim.

Claim 9 :

The composition which is manufactured by using the hydroxypropyl cellulose as to the first claim as the pododerm solution among the pododerm process.

Claim 10 :

The composition which is manufactured by using hydroxypropylmethylcellulose as to the first claim as the pododerm solution among the pododerm process.

Claim 11 :

The composition which is manufactured by dissolving to 10% concentration in solvent and using to 5 the hydroxypropyl cellulose as to claim 9 or the tenth claim, or hydroxypropylmethylcellulose.

Claim 12 :

Composition wherein as to the first claim, the refinement (tablet) or the pellet form.

Drawings

Fig. 1

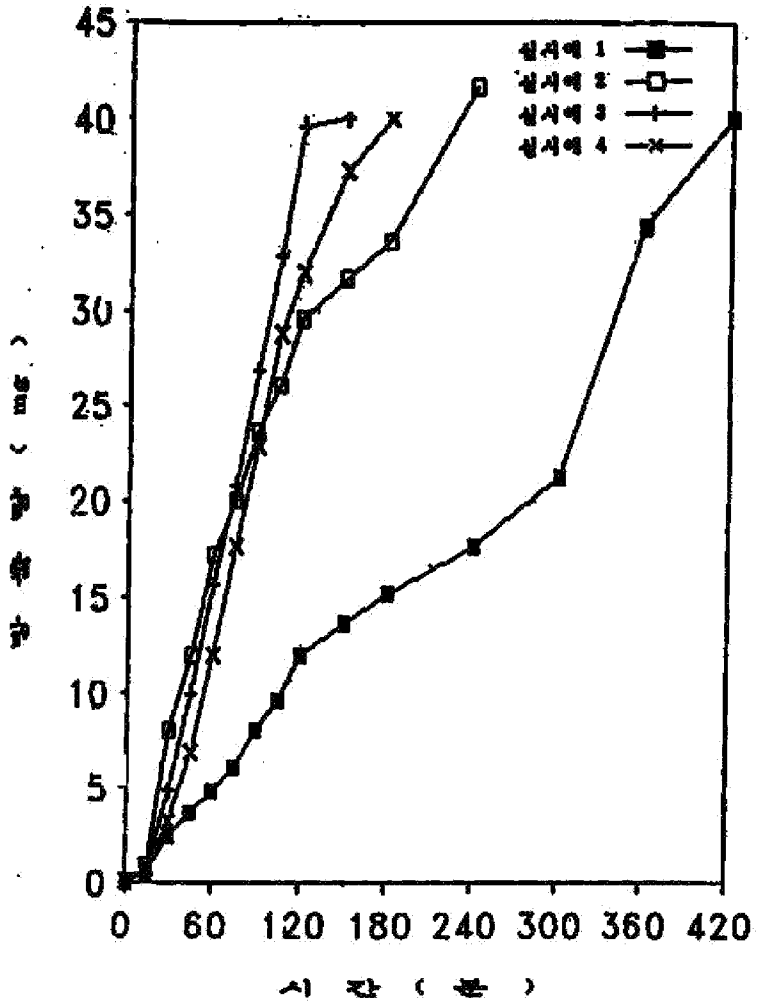

Fig. 2

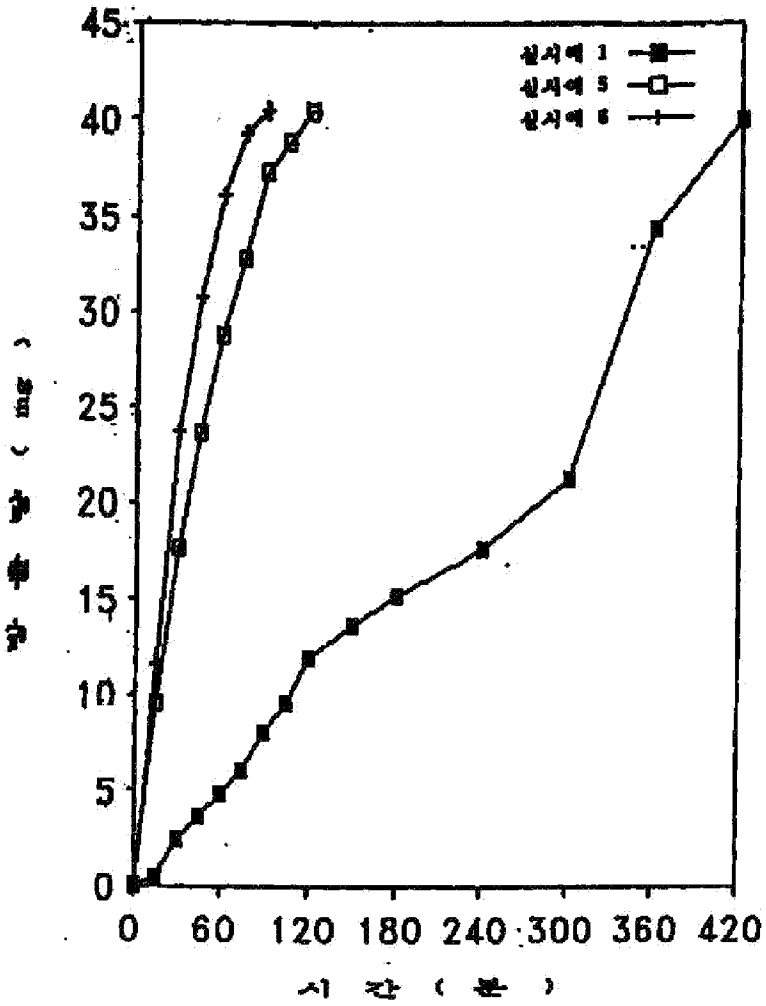

Fig. 3